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L9	L8 and (ER or RXR or RAR)	11	L9
L8	l1 and (transgen\$ or knockout)	51	L8
L7	L6 not l4	9	L7
L6	l1 and ER	12	L6
L5	L4 not l3	1	L5
L4	l1 and RXR	3	L4
L3	l1 and RAR	2	L3
L2	L1 near3 RAR	0	L2
L1	Cre near3 (fus\$ or ligat\$)	69	L1

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structures available in REGISTRY  
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NEWS 31 Apr 14 MEDLINE Reload  
NEWS 32 Apr 17 Polymer searching in REGISTRY enhanced  
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added to PHAR  
NEWS 37 May 15 MEDLINE file segment of TOXCENTER reloaded  
NEWS 38 May 15 Supporter information for ENCOMPAT and ENCOMPLIT updated  
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NEWS 40 May 19 Simultaneous left and right truncation added to WSCA  
NEWS 41 May 19 RAPRA enhanced with new search field, simultaneous left and  
right truncation  
  
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MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),  
AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003  
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=> s Cre (3a) (fus? or ligat?)  
L1 216 CRE (3A) (FUS? OR LIGAT?)

=> s I1 and (RXR or RAR or ER)  
L2 37 L1 AND (RXR OR RAR OR ER)

=> s I2 and (transgen? or knockout)  
L3 26 L2 AND (TRANSGEN? OR KNOCKOUT)

=> dup rem I3  
PROCESSING COMPLETED FOR L3  
L4 12 DUP REM L3 (14 DUPLICATES REMOVED)

=> d bib abs 1-  
YOU HAVE REQUESTED DATA FROM 12 ANSWERS - CONTINUE? Y(N):y

L4 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2003 ACS  
AN 2002:511498 CAPLUS  
DN 137:42577  
TI A \*\*\*transgenic\*\*\* mouse carrying a gene for a \*\*\*cre\*\*\*  
recombinase \*\*\*fusion\*\*\* protein regulated by synthetic estrogens  
IN Chambon, Pierre; Metzger, Daniel  
PA Association pour le Developpement de la Recherche en Genetique Moleculaire  
Aderegem, Fr.  
SO Fr. Demande, 141 pp.  
CODEN: FRXXBL  
DT Patent  
LA French  
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI FR 2814642	A1	20020405	FR 2000-12570	20001003
US 2002100088	A1	20020725	US 2001-853033	20010511
WO 2002028175	A2	20020411	WO 2001-182246	20010928
WO 2002028175	A3	20030109		
W. CA, JP				
FR, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				

PRAI FR 2000-12570 A 20001003  
US 2001-853033 A 20010511  
AB A \*\*\*transgenic\*\*\* non-human metazoan, specifically a mouse, that  
carries the gene for a \*\*\*fusion\*\*\* protein of \*\*\*cre\*\*\*  
recombinase and a nuclear estrogen receptor is described. The receptor is  
responsive to synthetic estrogens, such as tamoxifen, but not to natural  
estrogens and so can be used to regulate recombination via loxP sites,  
e.g. at different developmental stages, allowing the anal. of the role of  
a gene at these stages. Specifically, the method is used to investigate  
the function of retinoid X receptor .alpha. ( \*\*\*RXR\*\*\* .alpha.). The  
construction of the genes for \*\*\*RXR\*\*\* .alpha. contg. loxP sites and  
the \*\*\*Cre\*\*\* recombinase \*\*\*fusion\*\*\* protein with an estrogen  
receptor is described. The fusion protein gene was placed under the  
control of tissue-specific promoters to limit the deletions to specific  
tissues. \*\*\*Transgenic\*\*\* mice carrying these genes were constructed  
by std. methods. Inactivation of the \*\*\*RXR\*\*\* .alpha. gene in the  
epidermis resulted in alopecia and the development of cysts on the skin  
within 6-12 wk of administration of tamoxifen. The skin continued to  
degenerate and after 20 wk small wound-like lesions appeared.  
Inactivation of the \*\*\*RXR\*\*\* .alpha. gene in adipocytes appeared to be  
without phenotype.

L4 ANSWER 2 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

AN 2002:310362 BIOSIS  
DN PREV200200310362  
TI Ligand-dependent genetic recombination in fibroblasts: A potentially  
powerful technique for investigating gene function in fibrosis  
AU Zheng, Bing; Zhang, Zhaoping; Black, Carol M.; de Crombrugge, Benoit;  
Denton, Christopher P. (1)  
CS (1) Center for Rheumatology, University College London, Rowland Hill St.,  
Royal Free Campus, London, NW3 2PF; c.denton@rfc.ucl.ac.uk UK  
SO American Journal of Pathology, (May, 2002) Vol. 160, No. 5, pp. 1609-1617.  
http://ajp.amjpathol.org/. print.  
ISSN: 0002-9440.

DT Article  
LA English  
AB Strategies for conditional induction of \*\*\*transgene\*\*\* expression in  
mice are likely to be valuable for testing the role of candidate genes in  
disease pathogenesis. We have developed a system for lineage-specific,  
ligand-dependent, induction of sustained \*\*\*transgene\*\*\* expression in  
fibroblastic cells in mice using a chimeric gene encoding the \*\*\*Cre\*\*\*  
- \*\*\*ER\*\*\* (T) \*\*\*fusion\*\*\* protein, under the control of a  
fibroblast-specific regulatory sequence from the proalpha2(I)collagen  
gene. Cre- \*\*\*ER\*\*\* (T) operates as a tamoxifen-dependent DNA  
recombinase to excise fragments flanked by specific LoxP consensus  
sequences. To test efficiency and ligand dependency of this strategy, Cre-  
\*\*\*ER\*\*\* (T)-expressing mice were backcrossed with heterozygous  
ROSA26-LacZ reporter mice, in which a floxed-STOP cassette has been  
introduced upstream of a bacterial beta-galactosidase (LacZ) reporter gene  
at a ubiquitously expressed locus. Constitutive or tamoxifen-induced LacZ  
expression was examined in embryonic, neonatal, and adult compound-  
\*\*\*transgenic\*\*\* mice. When pregnant ROSA26-LacZ females received a  
single dose of tamoxifen, high-level expression of LacZ in the skin was  
demonstrable from 24 hours after injection in double- \*\*\*transgenic\*\*\*  
embryos harboring both the Cre- \*\*\*ER\*\*\* (T) \*\*\*transgene\*\*\* and the  
target ROSA26-LacZ allele. High-level expression of LacZ was also induced  
postnatally by tamoxifen specifically in dermal and visceral fibroblasts.  
By allowing efficient embryonic or postnatal modification of alleles that  
have been targeted to incorporate LoxP sites, or to switch on  
\*\*\*transgenes\*\*\* cloned downstream of the floxed-STOP cassette, this  
system will allow fibroblast-specific genetic perturbations to be induced  
at predetermined embryonic or postnatal time points. This should greatly  
assist in vivo functional studies of candidate genes in fibrotic  
diseases such as systemic sclerosis.

L4 ANSWER 3 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

AN 2002:298147 BIOSIS  
DN PREV200200298147  
TI Efficient recombination in diverse tissues by a tamoxifen-inducible form  
of Cre: A tool for temporally regulated gene activation/inactivation in  
the mouse.  
AU Hayashi, Shigemitsu; McMahon, Andrew P. (1)  
CS (1) Department of Molecular and Cellular Biology, Harvard University, 18  
Divinity Avenue, Cambridge, MA, 02138; amcmahon@mcmb.harvard.edu USA  
SO Developmental Biology, (April 15, 2002) Vol. 244, No. 2, pp. 305-318.  
http://www.academicpress.com/db. print.  
ISSN: 0012-1606.  
DT Article  
LA English  
AB In recent years, the Cre integrase from bacteriophage P1 has become an  
essential tool for conditional gene activation and/or inactivation in  
mouse. In an earlier report, we described a \*\*\*fusion\*\*\* protein  
between \*\*\*Cre\*\*\* and a mutated form of the ligand binding domain of  
the estrogen receptor (Cre-ERTM) that renders Cre activity tamoxifen (TM)

- inducible, allowing for conditional modification of gene activity in the mammalian neural tube in utero. In the current work, we have generated a "transgenic" mouse line in which Cre-ERTM is ubiquitously expressed to permit temporally regulated Cre-mediated recombination in diverse tissues of the mouse at embryonic and adult stages. We demonstrate that a single, intraperitoneal injection of TM into a pregnant mouse at 8.5 days postcoitum leads to detectable recombination in the developing embryo within 6 h of injection and efficient recombination of a reporter gene in derivatives of all three germ layers within 24 h of injection. In addition, by varying the dose of TM injected, the percentage of cells undergoing a recombination event in the embryo can be controlled. Dose-dependent excision induced by TM was also possible in diverse tissues in the adult mouse, including the central nervous system, and in cultured cells derived from the "transgenic" mouse line. This inducible Cre system will be a broadly useful tool to modulate gene activity in mouse embryos, adults, and culture systems where temporal control is an important consideration.
- L4 ANSWER 4 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3  
AN 2003:35107 BIOSIS  
DN PREV200300035107  
TI "ER" -based double iCre fusion protein allows partial recombination in forebrain.  
AU Casanova, Emilio (1); Fehsenfeld, Sandra; Lemberger, Thomas; Shimshek, Derya R.; Sprengel, Rolf; Mantamadiotis, Theo  
CS (1) Abteilung Molekularbiologie der Zelle I., Deutsches Krebsforschungszentrum (DKFZ), Im Neuenheimer Feld 280, D-69120, Heidelberg, Germany; e.casanova@dkfz.de Germany  
SO Genesis The Journal of Genetics and Development, (November 2002, 2002) Vol. 34, No. 3, pp. 208-214, print.  
ISSN: 1526-954X.  
DT Article  
LA English  
AB Here we describe the generation of a new tamoxifen-inducible double "Cre" "fusion" protein generated by fusing two ERT2 domains onto both ends of the iCre recombinase (a codon improved "Cre" recombinase). This "Cre" "fusion" protein (ERiCreER) had a twofold increased activity in cell culture assays than the previously described MerCreMer "Cre" double "fusion" protein. ERiCreER was targeted to the brain by placing it under the control of the promoter from the CamKIIalpha gene using a 170 kb BAC. The fusion protein was detected in hippocampus, cortex, striatum, thalamus, and hypothalamus but not in cerebellum. The ERiCreER was cytoplasmic in the absence of tamoxifen and translocated into the nucleus upon tamoxifen administration. The activity of the ERiCreER was tested in vivo by mating the CamKIIalpha ERiCreER "transgenic" line with mice harbouring exon 10 of the CREB gene flanked by two LoxP sites. In the absence of tamoxifen, no background activity was detected in mice older than 6 months. After tamoxifen administration, most if not all of the ERiCreER fusion protein translocated from the cytoplasm to the nucleus; however, only 5-10% of the "floxed" CREB allele was recombined. Recombination was also visualised at the cellular level by following the upregulation of the CREM protein, which corresponds precisely with CREB loss/recombination. Unlike in other tissues (Sohal et al., 2001; Tannour-Louet et al., 2002), it appears that in brain, although ERiCreER can bind tamoxifen, the Cre-recombinase cannot be fully activated.
- L4 ANSWER 5 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
AN 2002311838 EMBASE  
TI Temporal Cre-mediated recombination exclusively in endothelial cells using Tie2 regulatory elements.  
AU Forde A.; Constien R.; Grone H.-J.; Hammerling G.; Arnold B.  
CS B. Arnold, Department of Molecular Immunology, Division of Tumor Immunology, German Cancer Research Center, Heidelberg 69120, Germany; b.arnold@dkfz-heidelberg.de  
SO Genesis, (2002) 33/4 (191-197).  
Refs: 21  
ISSN: 1526-954X CODEN: GNEFSY  
CY United States  
DT Journal; Article  
FS 022 Human Genetics  
029 Clinical Biochemistry  
LA English  
SL English  
AB The versatility of the bacteriophage Cre/LoxP system is dependent on the availability of a spectrum of tissue-specific Cre "transgenic" mice to address a host of biological questions. In this paper, we report on the generation of an inducible Tie2Cre "transgenic" mouse line that facilitates gene targeting exclusively in endothelial cells. The temporal manner of recombination is feasible through the use of a "Cre" -estrogen receptor "fusion" protein "ER" (T2) and was, in practical terms, achieved by feeding the animals the estrogen antagonist tamoxifen orally for 5 weeks. High efficiency of recombination was found in the vast majority of endothelial cell populations examined, as monitored by an EGFP reporter mouse line. Critically, no EGFP expression was observed in any uninduced mice. This inducible Cre line will be a very beneficial asset to investigating the role of endothelial specific genes in the adult mouse and to induce "transgenes" in the endothelium in an extremely efficient manner. .COPYRG. 2002 Wiley-Liss, Inc.
- L4 ANSWER 6 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
AN 2001099876 EMBASE  
TI An efficient system for conditional gene expression in embryonic stem cells and in their in vitro and in vivo differentiated derivatives.  
AU Vallier L.; Mandip J.; Markossian S.; Lukasiewicz A.; Dehay C.; Metzger D.; Chambon P.; Samarut J.; Savatier P  
CS P. Savatier, Lab. de Biol. Moleculaire/Cellulaire, Ctr. Natl. de la Rech. Scientifique, Inst. Natl. Rech. Agronomique LA913, 48 Allée d'Italie, 69364 Lyon Cedex 07, France; Pierre.Savatier@Gens-lyon.fr  
SO Proceedings of the National Academy of Sciences of the United States of America, (27 Feb 2001) 98/5 (2487-2492).  
Refs: 32  
ISSN: 0027-8424 CODEN: PNASA6  
CY United States  
DT Journal; Article  
FS 004 Microbiology  
021 Developmental Biology and Teratology  
037 Drug Literature Index  
LA English  
SL English
- AB We have developed a universally applicable system for conditional gene expression in embryonic stem (ES) cells that relies on tamoxifen-dependent Cre recombinase-loxP site-mediated recombination and bicistronic gene-trap expression vectors that allow "transgene" expression from endogenous cellular promoters. Two vectors were introduced into the genome of recipient ES cells, successively: (i) a bicistronic gene-trap vector encoding the beta-galactosidase/neo(R) "fusion" protein and the "Cre" - "ER" (T2) ( "Cre" recombinase "fused" to a mutated ligand-binding domain of the human estrogen receptor) and (ii) a bicistronic gene-trap vector encoding the hygro(R) protein and the human alkaline phosphatase (hAP), the expression of which is prevented by tandemly repeated stop-of-transcription sequences flanked by loxP sites. In selected clones, hAP expression was shown to be regulated accurately by 4-hydroxy-tamoxifen. Strict hormone-dependent expression of hAP was achieved (i) in vitro in undifferentiated ES cells and embryoid bodies, (ii) in vivo in virtually all the tissues of the 10-day-old chimeric fetus (after injection of 4-hydroxy-tamoxifen to foster mothers), and (iii) ex vivo in primary embryonic fibroblasts isolated from chimeric fetuses. Therefore, this approach can be applied to drive conditional expression of virtually any "transgene" in a large variety of cell types, both in vitro and in vivo.
- L4 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2003 ACS  
AN 2001:47713 CAPLUS  
DN 135:147951  
TI Impaired adipogenesis and lipolysis in the mouse upon selective ablation of the retinoid X receptor. alpha. mediated by a tamoxifen-inducible chimeric Cre recombinase (Cre-ERT2) in adipocytes  
AU Imai, Takeshi; Jiang, Ming; Chambon, Pierre; Metzger, Daniel  
CS Institut de Genetique et de Biologie Moleculaire et Cellulaire, Centre National de la Recherche Scientifique/Institut National de la Sante et de la Recherche Medicale/Universite Louis Pasteur, College de France, Illkirch, 67404, Fr.  
SO Proceedings of the National Academy of Sciences of the United States of America (2001), 98(1), 224-228  
CODEN: PNASA6; ISSN: 0027-8424  
PB National Academy of Sciences  
DT Journal  
LA English  
AB Retinoid X receptor. alpha. ( "RXR" alpha.) is involved in multiple signaling pathways, as a heterodimeric partner of several nuclear receptors. To investigate its function in energy homeostasis, the authors have selectively ablated the "RXR" alpha. gene in adipocytes of 4-wk-old "transgenic" mice by using the tamoxifen-inducible Cre-ERT2 recombination system. Mice lacking "RXR" alpha. in adipocytes were resistant to dietary and chem. induced obesity and impaired in fasting-induced lipolysis. Our results also indicate that "RXR" alpha. is involved in adipocyte differentiation. Thus, the data demonstrate the feasibility of adipocyte-selective temporally controlled gene engineering and reveal a central role of "RXR" alpha. in adipogenesis, probably as a heterodimeric partner for peroxisome proliferator-activated receptor. gamma..
- RECENT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT
- L4 ANSWER 8 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4  
AN 2001:271557 BIOSIS  
DN PREV200100271557  
TI Site- and time-specific gene targeting in the mouse.  
AU Metzger, Daniel; Chambon, Pierre (1)  
CS (1) College de France, Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/ULP, 67404, Illkirch Cedex, C.U. de Strasbourg France  
SO Methods (Orlando), (May, 2001) Vol. 24, No. 1, pp. 71-80, print.  
ISSN: 1046-2023.  
DT Article  
LA English  
SL English  
AB The efficient introduction of somatic mutations in a given gene, at a given time, in a specific cell type, will facilitate studies of gene function and the generation of animal models for human diseases. We have established a conditional site-specific recombination system in mice using a new version of the Cre/lox system. The "Cre" recombinase has been "fused" to a mutated ligand binding domain of the human estrogen receptor ( "ER" ), resulting in a tamoxifen-dependent Cre recombinase, Cre-ERT, that is activated by tamoxifen, but not by estradiol. "Transgenic" mice were generated expressing Cre-ERT under the control of a cytomegalovirus promoter. Administration of tamoxifen to these "transgenic" mice induced excision of a chromosomally integrated gene flanked by loxP sites in a number of tissues, whereas no excision could be detected in untreated animals. However, the efficiency of excision varied between tissues, and the highest level (approx40%) was obtained in the skin. To determine the efficiency of excision mediated by Cre-ERT in a given cell type, Cre-ERT-expressing mice were crossed with reporter mice in which expression of Escherichia coli beta-galactosidase can be induced through Cre-mediated recombination. The efficiency and kinetics of this recombination were analyzed at the cellular level in the epidermis of 8- to 8-week-old double "transgenic" mice. Site-specific excision occurred within a few days of tamoxifen treatment in essentially all epidermis cells expressing Cre-ERT. These results indicate that cell-specific expression of Cre-ERT in "transgenic" mice can be used for efficient tamoxifen-dependent Cre-mediated recombination at loci containing loxP sites, to generate site-specific somatic mutations in a spatiotemporally controlled manner. This conditional site-specific recombination system should allow the analysis of "knockout" phenotypes that cannot be addressed by conventional gene targeting.
- L4 ANSWER 9 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5  
AN 2000:55232 BIOSIS  
DN PREV20000055232  
TI Temporally-controlled site-specific mutagenesis in the basal layer of the epidermis: Comparison of the recombinase activity of the tamoxifen-inducible Cre-ERT and Cre-ERT2 recombinases.  
AU Indra, Arup Kumar; Warot, Xavier; Brocard, Jacques; Bornert, Jean-Marc; Xiao, Jia-Hao; Chambon, Pierre (1); Metzger, Daniel  
CS (1) College de France, Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/ULP, 67404, Illkirch Cedex, C.U. de Strasbourg France  
SO Nucleic Acids Research, (Nov. 15, 1999) Vol. 27, No. 22, pp. 4324-4327.

ISSN: 0305-1048.

DT Article

LA English

SL English

AB Conditional DNA excision between two LoxP sites can be achieved in the mouse using **Cre** -ERT, a **Cre** protein between a mutated ligand binding domain of the human estrogen receptor (**ER**) and the Cre recombinase, the activity of which can be induced by 4-hydroxy-tamoxifen (OHT), but not natural **ER** ligands. We have recently characterized a new ligand-dependent recombinase, Cre-ERT2, which was approx 4-fold more efficiently induced by OHT than Cre-ERT in cultured cells. In order to compare the in vivo efficiency of these two ligand-inducible recombinases to generate temporally-controlled somatic mutations, we have engineered **transgenic** mice expressing a LoxP-flanked (floxed) **transgene** reporter and either Cre-ERT or Cre-ERT2 under the control of the bovine keratin 5 promoter that is specifically active in the epidermis basal cell layer. No background recombinase activity could be detected, while recombination was induced in basal keratinocytes upon OHT administration. Interestingly, a dose-response study showed that Cre-ERT2 was approx 10-fold more sensitive to OHT induction than Cre-ERT.

L4 ANSWER 10 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6

AN 1998:446923 BIOSIS

DN PREV199800446923

TI A chimeric Cre recombinase inducible by synthetic, but not by natural ligands of the glucocorticoid receptor.

AU Brocard, Jacques; Feil, Robert; Chambon, Pierre (1); Metzger, Daniel

CS (1) Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/ULP, Collège de France, BP 163, C.U. de Strasbourg, 67404 Illkirch Cedex France

SO Nucleic Acids Research, (Sept. 1, 1998) Vol. 26, No. 17, pp. 4088-4090. ISSN: 0305-1048.

DT Article

LA English

AB We have developed a new ligand-dependent chimeric recombinase (**Cre**-GRdx) by **fusing** the site-specific **Cre** recombinase to the ligand binding domain (LBD) of a mutant human glucocorticoid receptor (GRdx). The synthetic glucocorticoid receptor (GR) ligands dexamethasone, triamcinolone acetonide and RU38486 efficiently induce recombinase activity in F9 murine embryonal carcinoma cells expressing constitutively Cre-GRdx. In contrast, no recombinase activity was detected in the absence of ligand or in the presence of the natural GR ligands corticosterone, cortisol or aldosterone. Moreover, physiological concentrations of these natural GR ligands do not affect Cre-GRdx recombinase activity induced by dexamethasone. Thus, as previously shown using **Cre**-estrogen receptor (**ER**) **fusion** proteins, **Cre**-GRdx might be useful for achieving loxP site-directed mutagenesis in cultured cells and spatio-temporally controlled somatic cell mutagenesis in **transgenic** mice.

L4 ANSWER 11 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AN 1998028038 EMBASE

TI Spatio-temporally controlled site-specific somatic mutagenesis in the mouse.

AU Brocard J.; Ward X.; Wendling O.; Messadeg N.; Vonesch J.-L.; Chambon P.; Metzger D.

CS P. Chambon, Genetique/Biol. Molec./Cell. Inst., Centre National de la Recherche Sci., Université Louis Pasteur, 67404 Illkirch-Cedex, France. igbmc@igbmc.u-strasbg.fr

SO Proceedings of the National Academy of Sciences of the United States of America, (1997) 94/26 (14559-14563). Refs: 16

ISSN: 0027-8424 CODEN: PNASAB

CY United States

DT Journal; Article

FS 022 Human Genetics

029 Clinical Biochemistry

LA English

SL English

AB The efficient introduction of somatic mutations in a given gene, at a given time, in a specific cell type will facilitate studies of gene function and the generation of animal models for human diseases. We have shown previously that conditional recombination-excision between two loxP sites can be achieved in mice by using the **Cre** recombinase **fused** to a mutated ligand binding domain of the human estrogen receptor (Cre-**ER** (T)), which binds tamoxifen but not estrogens. DNA excision was induced in a number of tissues after administration of tamoxifen to **transgenic** mice expressing Cre-**ER** (T) under the control of the cytomegalovirus promoter. However, the efficiency of excision varied between tissues, and the highest level (simeq 40%) was obtained in the skin. To determine the efficiency of excision mediated by Cre-**ER** (T) in a given cell type, we have now crossed Cre-**ER** (T)-expressing mice with reporter mice in which expression of Escherichia coli .beta.-galactosidase can be induced through Cre-mediated recombination. The efficiency and kinetics of this recombination were analyzed at the cellular level in the epidermis of 8- to 8-week-old double **transgenic** mice. We show that site-specific excision occurred within a few days of tamoxifen treatment in essentially all epidermis cells expressing Cre-**ER** (T). These results indicate that cell-specific expression of Cre-**ER** (T) in **transgenic** mice can be used for efficient tamoxifen-dependent, Cre-mediated recombination at loci containing loxP sites to generate site-specific somatic mutations in a spatio-temporally controlled manner.

L4 ANSWER 12 OF 12 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7

AN 1998:508445 BIOSIS

DN PREV199899230801

TI Ligand-activated site-specific recombination in mice.

AU Feil, R.; Brocard, J.; Mascres, B.; Le Meur, M.; Metzger, D.; Chambon, P.

CS (1) Inst. Genet. Biol. Mol. Cell., Centre Natl. Recherche Scientifique, Inst. Natl. Santé Recherche Médicale, Univ. Louis Pasteur, Collège France, BP 163, 67404 Illkirch-Cedex, Strasbourg France

SO Proceedings of the National Academy of Sciences of the United States of America, (1998) Vol. 95, No. 20, pp. 10887-10890. ISSN: 0027-8424.

DT Article

LA English

AB Current mouse gene targeting technology is unable to introduce somatic

mutations at a chosen time and/or in a given tissue. We report here that conditional site-specific recombination can be achieved in mice using a new version of the Cre/lox system. The **Cre** recombinase has been **fused** to a mutated ligand-binding domain of the human estrogen receptor (**ER**) resulting in a tamoxifen-dependent Cre recombinase, Cre-**ER** (T), which is activated by tamoxifen, but not by estradiol. **Transgenic** mice were generated expressing Cre-**ER** (T) under the control of a cytomegalovirus promoter. We show that excision of a chromosomally integrated gene flanked by loxP sites can be induced by administration of tamoxifen to these **transgenic** mice, whereas no excision could be detected in untreated animals. This conditional site-specific recombination system should allow the analysis of **knockout** phenotypes that cannot be addressed by conventional gene targeting.

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COST IN U.S. DOLLARS	ENTRY	SINCE FILE	TOTAL
FULL ESTIMATED COST		SESSION	
		0.06	48.32

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	ENTRY	SINCE FILE	TOTAL
CA SUBSCRIBER PRICE		SESSION	
		0.00	-1.30

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=> d his

(FILE 'HOME' ENTERED AT 17:50:29 ON 04 JUN 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 17:50:37 ON 04 JUN 2003  
L1 216 S CRE (3A) (FUS? OR LIGAT?)  
L2 37 S L1 AND (RXR OR RAR OR ER)  
L3 26 S L2 AND (TRANSGEN? OR KNOCKOUT)  
L4 12 DUP REM L3 (14 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 17:58:54 ON 04 JUN 2003

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 17:57:44 ON 04 JUN 2003

=> s l2 not l3

L5 11 L2 NOT L3

=> dup rem l5

PROCESSING COMPLETED FOR L5  
L6 6 DUP REM L5 (5 DUPLICATES REMOVED)

=> d bib abs 1-

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L6 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1

AN 2003:198022 BIOSIS

DN PREV200300198022

TI A noninvasive genetic/pharmacologic strategy for visualizing cell morphology and clonal relationships in the mouse.

AU Badea, Tudor C.; Wang, Yanshu; Nathans, Jeremy (1)

CS (1) Johns Hopkins University School of Medicine, 725 North Wolfe Street, 805 Preclinical Teaching Building, Baltimore, MD, 21205, USA: jnathans@jhmi.edu USA

SO Journal of Neuroscience, (March 15 2003) Vol. 23, No. 6, pp. 2314-2322. print. ISSN: 0270-6474.

DT Article

LA English

AB Analysis of cellular morphology is the most general approach to neuronal classification. With the increased use of genetically engineered mice, there is a growing need for methods that can selectively visualize the morphologies of specified subsets of neurons. This capability is needed both to define cell morphologic phenotypes and to mark cells in a noninvasive manner for lineage studies. To this end, we describe a bipartite genetic system based on a **Cre**-estrogen receptor (**ER**) **fusion** protein that irreversibly activates a plasma membrane-bound alkaline phosphatase reporter gene by site-specific recombination. Because the efficiency and timing of gene rearrangement is controlled pharmacologically, a sparse subset of labeled cells can be generated from the set of CreER-expressing cells at any time during development. Histochemical visualization of alkaline phosphatase activity reveals neuronal morphology with strong and uniform labeling of all processes.

L6 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2000:365138 BIOSIS

DN PREV200000365138

TI Temporally-controlled site-specific mutagenesis in the adult mouse brain.

AU Weber, P. (1); Metzger, D. (1); Chambon, P. (1)

CS (1) IGBMC, Illkirch France  
SO European Journal of Neuroscience, (2000) Vol. 12, No. Supplement 11, pp. 172, print.  
Meeting Info.: Meeting of the Federation of European Neuroscience Societies Brighton, UK June 24-28, 2000  
ISSN: 0953-816X.  
DT Conference  
LA English  
SL English

L6 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
AN 1999:299609 BIOSIS  
DN PREV199900299609  
TI Competition by exogenous estrogen receptor ( \*\*\*ER\*\*\* ) ligand binding domain results in leakiness from a \*\*\*Cre\*\*\* - \*\*\*ER\*\*\*  
\*\*\*fusion\*\*\* protein.  
AU Gardner, Thomas W. (1); Harrison, David J. (1); Clarke, Alan R. (1)  
CS (1) CRC Laboratories, Department of Pathology, University of Edinburgh Medical School, Teviot Place, Edinburgh, EH8 9AG UK  
SO Journal of Pathology, (1999) Vol. 187, No. SUPPL., pp. 23A.  
Meeting Info.: 17th Meeting of the Pathological Society of Great Britain and Ireland Cambridge, England, UK January 6-8, 1999 Pathological Society of Great Britain and Ireland  
ISSN: 0022-3417.  
DT Conference  
LA English

L6 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS  
AN 1997:211268 CAPLUS  
DN 128:198099  
TI Helper viruses containing recombination sites flanking a gene necessary for viral propagation and their use for preparing recombinant replication-deficient viral vectors  
IN Lusky, Monika; Mehtali, Majid  
PA Transgene S.A., Fr.; Lusky, Monika; Mehtali, Majid  
SO PCT Int. Appl., 43 pp.  
CODEN: PIXXD2  
DT Patent  
LA French  
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9705255	A2	19970213	WO 1996-FR1200	19960730
WO 9705255	A3	19970306		
W: AU, CA, JP, SG, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
FR 2737501	A1	19970207	FR 1995-9289	19950731
FR 2737501	B1	19971024		
CA 2225551	AA	19970213	CA 1996-2225551	19960730
AU 9667044	A1	19970228	AU 1996-67044	19960730
AU 715487	B2	20000203		
EP 842279	A2	19980520	EP 1996-927107	19960730
EP 842279	B1	20011031		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11510049	T2	19990907	JP 1996-507291	19960730
EP 1132478	A2	20010912	EP 2001-108475	19960730
EP 1132478	A3	20020904		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 207959	E	20011115	AT 1996-927107	19960730
ES 2164910	T3	20020301	ES 1996-927107	19960730
US 9066478	A	20000523	US 1996-11257	19960309
US 9350575	B1	20020228	US 2000-563239	20000502
US 2002072120	A1	20020613	US 2001-920932	20010803
PRAI FR 1995-9289	A	19950731		
EP 1996-927107	A3	19960730		
WO 1996-FR1200	W	19960730		
US 1996-11257	A1	19980309		
US 2000-563239	A1	20000502		

AB Novel helper vectors are provided for complementing defective recombinant viral vectors, characterized in that they are provided with recombination sequences recognized by a recombinase. A complementation cell expressing the recombinase, and a method for prep. recombinant viral vectors as infectious viral particles for transferring and expressing genes of interest in a host organism or cell, are also provided. The invention is particularly suitable for use in gene therapy, esp. in humans. Adenoviral vector pTG4707 contg. an encapsidation signal flanked by loxP sites and lacking genes E1, E3 and E4 was constructed. Complementing cells 293/CRE-\*\*\*ER\*\*\*, which are 293 cells transformed with a plasmid expressing an estradiol receptor-\*\*\*Cre\*\*\* recombinase \*\*\*fusion\*\*\* protein were also prep. 293/CRE-\*\*\*ER\*\*\* cells transfected with pTG4707 and an E4-contg. retroviral vector are cultured to produce a mixed population of viral particles. Estradiol is then introduced into the medium to activate the Cre recombinase and inhibit formation of viral particles. Viral vectors enriched in the desired vectors, i.e. contg. fewer helper viruses relative to prior art viral vector preps., are obtained.

L6 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2  
AN 1997:452452 BIOSIS  
DN PREV199799751855  
TI Regulation of Cre recombinase activity by mutated estrogen receptor ligand-binding domains.  
AU Feil, Robert; Wagner, Juergen; Metzger, Daniel; Chambon, Pierre (1)  
CS (1) Inst. Genetique Biol. Mol. Cell., CNRS/INSERM/WULP, Coll. France, BP 163, 67404 Illkirch-Cedex, C.U. de Strasbourg France  
SO Biochemical and Biophysical Research Communications, (1997) Vol. 237, No. 3, pp. 752-757.  
ISSN: 0006-291X.  
DT Article  
LA English

AB Ligand-dependent chimeric Cre recombinases are powerful tools to induce specific DNA rearrangements in cultured cells and in mice. We report here the construction and characterization of a series of chimeric recombinases, each consisting of \*\*\*Cre\*\*\* fused\*\*\* to a mutated human oestrogen receptor (\*\*\*ER\*\*\* ) ligand-binding domain (LBD). Two new ligand-dependent recombinases which contain either the G400V/M543A/L544A or the G400V/L539A/L540A triple mutation of the human \*\*\*ER\*\*\* LBD are efficiently induced by the synthetic \*\*\*ER\*\*\* antagonists 4-hydroxytamoxifen (OHT) and ICI 162,780 (ICI), respectively, but are insensitive to 17-beta-oestradiol (E2). Both chimeric recombinases should be useful for efficient spatio-temporally controlled site-directed

somatic mutagenesis.

L6 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3  
AN 1995:408417 BIOSIS  
DN PREV199598422717  
TI Conditional site-specific recombination in mammalian cells using a ligand-dependent chimeric Cre recombinase.  
AU Metzger, Daniel; Clifford, John; Chiba, Hideki; Chambon, Pierre  
CS Inst. de Genet. et de Biologie Moleculaire et Cellulaire, Cent. Natl. de la Recherche Sci., Inst. Natl. de la Sante et de la Recherche Med., Universite Louis Pasteur, Coll. de France, 67404 Illkirch-Cedex, C.U. de Strasbourg France  
SO Proceedings of the National Academy of Sciences of the United States of America, (1995) Vol. 92, No. 15, pp. 6991-6995.  
ISSN: 0027-8424.  
DT Article  
LA English

AB We have developed a strategy to generate mutant genes in mammalian cells in a conditional manner by employing a \*\*\*fusion\*\*\* protein, \*\*\*Cre\*\*\* - \*\*\*ER\*\*\*, consisting of the loxP site-specific Cre recombinase linked to the ligand-binding domain of the human estrogen receptor. We have established homozygous retinoid X receptor alpha-negative (\*\*\*RXR\*\*\* -alpha-/-) F9 embryonal carcinoma cells constitutively expressing Cre-\*\*\*ER\*\*\* and have shown that estradiol or the estrogen agonist/antagonist 4-hydroxytamoxifen efficiently induced the recombinase activity, whereas no activity was detected in the absence of ligand or in the presence of the antiestrogen ICI 164,384. Furthermore, using a targeting vector containing a selection marker flanked by loxP sites, we have inactivated one retinoid acid receptor allele in such a line, demonstrating that the presence of the recombinase does not inhibit homologous recombination. Combining this conditional site-specific recombination system with tissue-specific expression of Cre-\*\*\*ER\*\*\* may allow modification of the mammalian genome in vivo in a spatiotemporally regulated manner.

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FULL ESTIMATED COST 0.12 64.59

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE TOTAL  
ENTRY SESSION  
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NEWS 5 Aug 19 Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN  
NEWS 6 Aug 28 Sequence searching in REGISTRY enhanced  
NEWS 7 Sep 03 JAPIO has been reloaded and enhanced  
NEWS 8 Sep 16 Experimental properties added to the REGISTRY file  
NEWS 9 Sep 16 CA Section Thesaurus available in CAPLUS and CA  
NEWS 10 Oct 01 CASREACT Enriched with Reactions from 1907 to 1985  
NEWS 11 Oct 24 BEILSTEIN adds new search fields  
NEWS 12 Oct 24 NUTRACEUTICALS International (NUTRACEUT) now available on STN  
NEWS 13 Nov 18 NUKIT has been renamed APOLLIT  
NEWS 14 Nov 25 More calculated properties added to REGISTRY  
NEWS 15 Dec 04 CSA files on STN  
NEWS 16 Dec 17 PCTFULL now covers WPI/PCT Applications from 1978 to date  
NEWS 17 Dec 17 TOXCENTER enhanced with additional content  
NEWS 18 Dec 17 Adis Clinical Trials Insight now available on STN  
NEWS 19 Jan 29 Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC  
NEWS 20 Feb 13 CANCERLIT is no longer being updated  
NEWS 21 Feb 24 METADEX enhancements

results in an increase in liver peroxisome number, marked hepatomegaly and induction of several genes encoding peroxisomal and other microsomal and mitochondrial enzymes involved in fatty acid metabolism. Chronic treatment of rodents with PP results in hepatocellular carcinoma. Species differences in PP responses have been found. For example, PP such as clofibrate and gemfibrozil, are highly effective lipid and cholesterol lowering drugs in humans but do not cause peroxisome proliferation and there is no evidence for increased liver cancers in patients receiving these drugs. A receptor, designated PP-activated receptor alpha (PPAR-alpha) is capable of trans-activating reporter genes containing a PP response (PPRE), but requires the presence of both PP, 9-cis retinoic acid and another receptor called RXR (retinoid X receptor). However, PP may not directly bind to PPAR-alpha but probably indirectly disturb cellular metabolism to liberate an endogenous ligand. Subsequent to the first identification of a PPAR-alpha, other members of this receptor family were found and designated PPAR-alpha, PPAR-beta (also called NUC1 and PPAR-delta) and PPAR-gamma. The alpha form is most abundant in liver and kidney, sites of peroxisome proliferation while the other two receptors are not significantly expressed in these tissues. On the basis of tissue-specific localization and spectrum of target gene activation, the physiological function of PPAR-alpha and PPAR-gamma appear to be related to fatty acid metabolism and regulation of adipogenesis, respectively. To gain insight into the function of PPAR-alpha and its role in the peroxisome proliferator response and hepatocellular carcinogenesis, gene targeting was used to develop a PPAR-alpha-deficient mouse. These animals are resistant to the pleiotropic effects of PP and no induction of any known target gene has been found. Recent studies on the phenotypes of these mice have led to an understanding of the mechanism of action of PP. They have also provided a useful model to establish the physiological role of PPAR-alpha in fatty acid homeostasis and inflammation.

L6 ANSWER 5 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
AN 1997:346448 BIOSIS  
DN PREV199799645651  
TI Decreased expression of murine PPAR-gamma in adipose tissue during endotoxemia.  
AU Hill, Molly R.; Young, Misty D.; McCurdy, Caren M.; Gimble, Jeffrey M.  
CS Dep. Radiologic Technology, Univ. Okla. Health Sciences Cent., 801 NE 13th Street, Oklahoma City, OK 73190 USA  
SO Endocrinology, (1997) Vol. 138, No. 7, pp. 3073-3078.  
ISSN: 0013-7227.  
DT Article  
LA English  
AB Infection-induced hyperlipidemia develops due to a combination of factors, one of which is decreased clearance of lipids from the bloodstream due to depressed synthesis of lipoprotein lipase (LPL). Recently, the peroxisome proliferator activated receptors (PPARs) have been shown to be important in the regulation of LPL, particularly PPAR-gamma. PPAR-gamma and its heterodimerization partner, RXR, have been shown to be transcriptional activators of LPL in co-transfection analysis. Therefore, we hypothesized that the decrease in LPL expression during endotoxemia may be a result of depressed PPAR-gamma expression. In these studies, we examined the effect of endotoxin or its proximal mediator, tumor necrosis factor (TNF), on the expression of PPAR-gamma in white (WAT) and brown adipose tissue (BAT) in CD-1 mice. We report that treatment with endotoxin, but not TNF, transiently decreased PPAR-gamma mRNA levels 4 hr after treatment. However, endotoxin or TNF treatment decreased PPAR-gamma protein levels after 18 hr, which was at a time when LPL mRNA levels were also depressed. These data suggest that decreased PPAR-gamma expression following endotoxin or TNF treatment may contribute to the hyperlipidemia due to decreased expression of LPL, which would impair triglyceride clearance.

L6 ANSWER 6 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
AN 1997:185734 BIOSIS  
DN PREV199799484937  
TI Differential PPAR-gamma-2 and RXR expression in the differentiating 3T3-L1 adipocyte.  
AU Thuillier, Philippe; Baillie, Rebecca; Clarke, Steven D.  
CS Univ. Texas, Austin, TX 78712 USA  
SO FASEB Journal, (1997) Vol. 11, No. 3, pp. A353.  
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 97 New Orleans, Louisiana, USA April 8-9, 1997  
ISSN: 0892-6638.  
DT Conference; Abstract  
LA English

L6 ANSWER 7 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
AN 1997:70483 BIOSIS  
DN PREV199799369886  
TI Terminal differentiation of human liposarcoma cells induced by ligands for peroxisome proliferator-activated receptor gamma and the retinoid X receptor.  
AU Tontonoz, Peter (1); Singer, Samuel; Forman, Barry M.; Sarraf, Pasha; Fletcher, Jonathan A.; Fletcher, Christopher D. M.; Brun, Regina P.; Mueller, Elisabeth; Altok, Soner; Oppenheim, Heather; Evans, Ronald M.; Spiegelman, Bruce M.  
CS (1) Gene Expression Lab., The Salk Inst. Biological Studies, La Jolla, CA 92037 USA  
SO Proceedings of the National Academy of Sciences of the United States of America, (1997) Vol. 94, No. 1, pp. 237-241.  
ISSN: 0027-8424.  
DT Article  
LA English  
AB Induction of terminal differentiation represents a promising therapeutic approach to certain human malignancies. The peroxisome proliferator-activated receptor gamma (PPAR-gamma) and the retinoid X receptor alpha (RXR-alpha) form a heterodimeric complex that functions as a central regulator of adipocyte differentiation. Natural and synthetic ligands for both receptors have been identified. We demonstrate here that PPAR-gamma is expressed at high levels in each of the major histologic types of human liposarcoma. Moreover, primary human liposarcoma cells can be induced to undergo terminal differentiation by treatment with the PPAR-gamma ligand pioglitazone, suggesting that the differentiation block in these cells can be overcome by maximal activation of the PPAR pathway. We further demonstrate that RXR-specific ligands are also potent adipogenic agents in cells expressing the PPAR-gamma/RXR heterodimer, and that simultaneous treatment of liposarcoma cells with both PPAR-gamma and RXR-specific ligands results in an additive stimulation of differentiation. Liposarcoma cell differentiation is characterized by accumulation of intracellular lipid, induction of adipocyte-specific genes, and withdrawal from the

cell cycle. These results suggest that PPAR-gamma ligands such as thiazolidinediones and RXR-specific retinoids may be useful therapeutic agents for the treatment of liposarcoma.

L6 ANSWER 8 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
AN 1998:384502 BIOSIS  
DN PREV199899088858  
TI A human peroxisome-proliferator-activated receptor-gamma is activated by inducers of adipogenesis, including thiazolidinedione drugs.  
AU Lambe, Kevin G.; Tugwood, Jonathan D. (1)  
CS (1) Res. Toxicol. Section, Zeneca Central Toxicology Lab., Alderley Park, Macclesfield, Cheshire SK10 4TJ UK  
SO European Journal of Biochemistry, (1998) Vol. 239, No. 1, pp. 1-7.  
ISSN: 0014-2958.  
DT Article  
LA English  
AB We have cloned a human cognate of the mouse peroxisome-proliferator-activated receptor-gamma (hPPAR-gamma) from a human placenta cDNA library. Sequence analysis reveals a high degree of similarity with the mouse receptor and, like other PPAR, hPPAR-gamma forms heterodimers with the retinoid X receptor (RXR) (RXR-gamma) and binds in vitro to DNA elements containing direct repeats of the sequence TGACCT. In common with mouse PPAR-gamma, hPPAR-gamma is expressed strongly in adipose tissue, but significant levels also are detectable in placenta, lung and ovary. In vitro trans-activation data suggest hPPAR-gamma is only poorly activated by xenobiotic peroxisome proliferators, although certain fatty acids and eicosanoids are potent activators of this receptor. Both mouse and human PPAR-gamma are capable of being activated by thiazolidinedione drugs, although the two receptors appear to differ in their sensitivity to these compounds. Taken together, these data suggest a high degree of structural and functional similarity between mouse and human PPAR-gamma, and provide evidence for variation in human receptor structure which may result in differential sensitivity to activators.

L6 ANSWER 9 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
AN 1995:510753 BIOSIS  
DN PREV199598515803  
TI cDNA cloning and characterization of the transcriptional activities of the hamster peroxisome proliferator-activated receptor hPPAR-gamma.  
AU Aperio, Christel; Pogoniec, Philippe; Saladin, Regis; Auwerx, Johan (1); Boulikos, Kim E.  
CS (1) Inst. Pasteur Lille, 1 rue Calmette, 59019 Lille France  
SO Gene (Amsterdam), (1995) Vol. 162, No. 2, pp. 297-302.  
ISSN: 0378-1119.  
DT Article  
LA English  
AB We have isolated a cDNA corresponding to the hamster peroxisome proliferator-activated receptor hPPAR-gamma, a member of the steroid nuclear hormone receptor superfamily of transcription factors. hPPAR-gamma mRNA is highly expressed in adipose tissue, and is expressed in lung, heart, kidney, liver and spleen to a lower extent. Thus, hPPAR-gamma may function in activating the transcription of target genes in a variety of tissues, including those not particularly subjected to peroxisomal beta-oxidation. hPPAR-gamma binds efficiently in the presence of retinoid X receptor (RXR) (RXR-gamma) to a peroxisome proliferator response element (PPRE) first identified in the acyl-CoA oxidase (ACO) promoter, the rate-limiting enzyme of peroxisomal beta-oxidation. The gene (ACO) encoding this enzyme has been previously shown to be under the transcriptional control of mouse PPAR (mPPAR). Although binding of hPPAR-gamma/RXR-gamma on the PPRE of the ACO promoter in vitro is similar to that observed for mPPAR/RXR-gamma, we show that the transcriptional activities of mPPAR and hPPAR-gamma are regulated differently in vivo in response to peroxisome proliferators and heterodimerization with RXR.

L6 ANSWER 10 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
AN 1995:387777 BIOSIS  
DN PREV199598402077  
TI The combine effect of two transcription factors c/EBP- alpha and RXR/PPAR-gamma-2 stimulates adipogenesis in fibroblasts.  
AU Vasseur-Cognet, Mireille  
SO M-S (Medicine Sciences), (1995) Vol. 11, No. 4, pp. 625-626.  
ISSN: 0767-0974.  
DT Article  
LA French

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 NEWS 24 Feb 28 NTIS now allows simultaneous left and right truncation  
 NEWS 25 Feb 28 PCTFULL now contains images  
 NEWS 26 Mar 04 SDI PACKAGE for monthly delivery of multiple SDI results  
 NEWS 27 Mar 20 EVENTLINE will be removed from STN  
 NEWS 28 Mar 24 PATDPAFULL now available on STN  
 NEWS 29 Mar 24 Additional information for trade-named substances without structures available in REGISTRY  
 NEWS 30 Apr 11 Display formats in DGENE enhanced  
 NEWS 31 Apr 14 MEDLINE Reload  
 NEWS 32 Apr 17 Polymer searching in REGISTRY enhanced  
 NEWS 33 Apr 21 Indexing from 1947 to 1956 being added to records in CA/CAPLUS  
 NEWS 34 Apr 21 New current-awareness alert (SDI) frequency in WPIDS/MPINDEX/WPIX  
 NEWS 35 Apr 28 RDISCLOSURE now available on STN  
 NEWS 36 May 06 Pharmacokinetic information and systematic chemical names added to PHAR  
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 NEWS 42 Jun 08 Simultaneous left and right truncation added to CBNB  
 NEWS 43 Jun 08 PASCAL enhanced with additional data

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=> s adipo? and RXR  
 L1 324 ADIPO? AND RXR

=> s RXR (3a) alpha  
 L2 2709 RXR (3A) ALPHA

=> s adipo?  
 L3 125860 ADIPO?

=> s i3 and i2  
 L4 133 L3 AND L2

=> dup rem i4  
 PROCESSING COMPLETED FOR L4  
 L5 77 DUP REM L4 (56 DUPLICATES REMOVED)

=> s i5 and py<=2000  
 1 FILES SEARCHED...  
 L6 50 L5 AND PY<=2000

=> d bib abs

L6 ANSWER 1 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 2000:335743 BIOSIS  
 DN PREV200000335743  
 TI A PPARgamma mutant serves as a dominant negative inhibitor of PPAR signaling and is localized in the nucleus.  
 AU Berger, Joel (1); Patel, Hansa V.; Woods, John; Hayes, Nancy S.; Parent, Stephen A.; Clemas, Joseph; Lebowitz, Mark D.; Elbrecht, Alex; Rachubinski, Richard A.; Capone, John P.; Moller, David E.  
 CS (1) Department of Molecular Endocrinology, Merck Research Laboratories, RY80N-C31, 128 E. Lincoln Avenue, Rahway, NJ, 07065 USA  
 SO Molecular and Cellular Endocrinology, ( \*\*\*April 25, 2000\*\*\* ) Vol. 162, No. 1-2, pp. 67-67, print.  
 ISSN: 0303-7207.

DT Article  
 LA English  
 SL English  
 AB The peroxisomal proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily that act as ligand-activated transcription factors. PPARgamma plays a critical role in regulating \*\*\*adipocyte\*\*\* differentiation and lipid metabolism. Recently, thiazolidinedione (TZD) and select non-TZD antidiabetic agents have been identified as PPARgamma agonists. To further characterize this receptor subclass, a mutant hPPARgamma lacking five carboxy-terminal amino acids was produced (hPPARgamma2DELTA500). In COS-1 cells transfected with PPAR-responsive reporter constructs, the mutant receptor could not be

activated by a potent PPARgamma agonist. When cotransfected with hPPARgamma2 or hPPARalpha, hPPARgamma2DELTA500 abrogated wild-type receptor activity in a dose-responsive manner. hPPARgamma2DELTA500 was also impaired with respect to binding of a high-affinity radioligand. In addition, its conformation was unaffected by normally saturating concentrations of PPARgamma agonist as determined by protease protection experiments. Electrophoretic mobility shift assays demonstrated that hPPARgamma2DELTA500 and hPPARgamma2 both formed heterodimeric complexes with human retinoid X receptor alpha (hRXRalpha) and could bind a peroxisome proliferator-responsive element (PPRE) with similar affinity. Therefore, hPPARgamma2DELTA500 appears to repress PPAR activity by competing with wild type receptor to dimerize with RXR and bind the PPRE. In addition, the mutant receptor may titrate out factors required for PPAR-regulated transcriptional activation. Both hPPARgamma2 and hPPARgamma2DELTA500 localized to the nucleus of transiently transfected COS-1 cells as determined by immunofluorescence using a PPARgamma-specific antibody. Thus, nuclear localization of PPARgamma occurs independently of its activation state. The dominant negative mutant, hPPARgamma2DELTA500, may prove useful in further studies to characterize PPAR functions both in vitro and in vivo

=> d bib abs 2

L6 ANSWER 2 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 2000:314239 BIOSIS  
 DN PREV200000314239  
 TI Sterol upregulation of human CETP expression in vitro and in transgenic mice by an LXR element.  
 AU Luo, Yi; Tall, Alan R. (1)  
 CS (1) Division of Molecular Medicine, Department of Medicine, Columbia University, New York, NY, 10032 USA  
 SO Journal of Clinical Investigation, ( \*\*\*February, 2000\*\*\* ) Vol. 105, No. 4, pp. 513-520, print.  
 ISSN: 0021-9738.

DT Article  
 LA English  
 SL English  
 AB The cholesterol ester transfer protein (CETP) facilitates the transfer of HDL cholesterol esters from plasma to the liver. Transgenic mice expressing human CETP, controlled by its natural flanking region, increase expression of this gene in response to hypercholesterolemia. We established a CETP promoter-luciferase reporter assay in differentiated 3T3-L1 \*\*\*adipocytes\*\*\* to map the sterol upregulatory element. Promoter mutagenesis suggested that a direct repeat of a nuclear receptor binding sequence separated by 4 nucleotides (DR4 element, -384 to -399) was responsible for this activity. Using mice carrying normal or mutated promoter sequences, we confirmed the importance of this element for gene induction by dietary sterol. A gel retardation complex containing LXRA/RXR was identified using the CETP DR4 element and \*\*\*adipocyte\*\*\* nuclear extracts. Both LXRA/RXRalpha and LXRBeta/RXRalpha transactivated the CETP promoter via its DR4 element in a sterol-responsive fashion. Thus, the positive sterol response of the CETP gene is mediated by a nuclear receptor binding site that is activated by LXRs. That Cyp7a, the rate-limiting enzyme for conversion of cholesterol into bile acids in the liver, is also regulated by LXRA/RXR suggests that this class of nuclear receptor coordinates the regulation of HDL cholesterol ester catabolism and bile acid synthesis in the liver.

=> d bib abs 3

L6 ANSWER 3 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 1998:492788 BIOSIS  
 DN PREV199800492788  
 TI A novel 3T3-L1 preadipocyte variant that expresses PPARgamma2 and RXRalpha but does not undergo differentiation.  
 AU Baillet, Rebecca A.; Sha, Xiaoming; Thuillier, Philippe; Clarke, Steven D. (1)  
 CS (1) Inst. Mol. Biol., Univ. Tex., Austin, TX 78712 USA  
 SO Journal of Lipid Research, ( \*\*\*Oct., 1998\*\*\* ) Vol. 39, No. 10, pp. 2046-2053  
 ISSN: 0022-2275.

DT Article  
 LA English  
 AB This report describes a novel \*\*\*adipocyte\*\*\*-like cell line termed 3T3-L1/RB1 that was derived from preadipocyte cell line, 3T3-L1. The 3T3-L1/RB1 cells continued to divide after reaching confluence, formed foci, and constitutively expressed a low level of \*\*\*adipose\*\*\* fatty acid binding protein (A-FABP) mRNA. However, 3T3-L1/RB1 cells did not undergo terminal differentiation as indicated by the failure of insulin and thiazolidinediones to induce the expression of A-FABP, lipoprotein lipase, and fatty acid synthase. We hypothesized that the 3T3-L1/RB1 variant did not respond to differentiation stimuli because it did not express either peroxisomal proliferator-activated receptor gamma2 (PPARgamma2) or its heterodimer partner, retinoid X receptor alpha (RXRalpha). Surprisingly, Western blots revealed that 3T3-L1/RB1 cells contained both PPARgamma2 and RXRalpha proteins at levels equal to or greater than that of the parent cell line. However, gel retardation assays using the \*\*\*adipose\*\*\* response element from A-FABP and nuclear protein extracts from 3T3-L1/RB1 cells treated with insulin or pioglitazone revealed that nuclear protein extracts from 3T3-L1/RB1 cells had very little ability to bind the PPARgamma2 recognition sequence of the A-FABP gene. These data suggest that the 3T3-L1/RB1 variant contains a mutation that may prevent ligand activation of PPARgamma2, and the subsequent conversion of 3T3-L1/RB1 cells to mature fat cells.

=> d bib abs 4-10

L6 ANSWER 4 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.  
 AN 1997:368218 BIOSIS  
 DN PREV1997368218  
 TI Recent update on the PPAR-alpha-null mouse.  
 AU Gonzalez, F. J.  
 CS Lab. Metabolism, Div. Basic Sci., Natl. Cancer Inst., Build. 37, Room 3E-24, NIH, Bethesda, MD 20892 USA  
 SO Biochimie (Paris), (1997) Vol. 79, No. 2-3, pp. 139-144.  
 ISSN: 0300-9084.  
 DT Journal; Article  
 LA English  
 AB Short-term treatment of rats and mice with peroxisome proliferators (PP)